



## Review Article/Artigo de Revisão

# Insights into the clinical and functional significance of cardiac autonomic dysfunction in Chagas disease

Considerações sobre o significado clínico-funcional da disfunção autonômica cardíaca na doença de Chagas

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### ABSTRACT

**Introduction:** Exclusive or associated lesions in various structures of the autonomic nervous system occur in the chronic forms of Chagas disease. In the indeterminate form, the lesions are absent or mild, whereas in the exclusive or combined heart and digestive disease forms, they are often more pronounced. Depending on their severity these lesions can result mainly in cardiac parasympathetic dysfunction but also in sympathetic dysfunction of variable degrees. Despite the key autonomic effect on cardiovascular functioning, the pathophysiological and clinical significance of the cardiac autonomic dysfunction in Chagas disease remains unknown.

**Methods:** Review of data on the cardiac autonomic dysfunction in Chagas disease and their potential consequences, and considerations supporting the possible relationship between this disturbance and general or cardiovascular clinical and functional adverse outcomes. **Results:** We hypothesise that possible consequences that cardiac dysautonomia might variably occasion or predispose in Chagas disease include: transient or sustained arrhythmias, sudden cardiac death, adverse overall and cardiovascular prognosis with enhanced morbidity and mortality, an inability of the cardiovascular system to adjust to functional demands and/or respond to internal or external stimuli by adjusting heart rate and other hemodynamic variables, and immunomodulatory and cognitive disturbances. **Conclusions:** Impaired cardiac autonomic modulation in Chagas disease might not be a mere epiphenomenon without significance. Indirect evidences point for a likely important role of this alteration as a primary predisposing or triggering cause or mediator favouring the development of subtle or evident secondary cardiovascular functional disturbances and clinical consequences, and influencing adverse outcomes.

**Keywords:** Chagas heart disease. Indeterminate form of Chagas disease. Heart autonomic control. Cardiac autonomic dysfunction. Cardiovascular outcomes.

### RESUMO

**Introdução:** Lesões isoladas ou combinadas de várias estruturas do sistema nervoso autônomo ocorrem nas formas crônicas da doença de Chagas. Na forma indeterminada, as lesões são discretas e podem estar até ausentes, enquanto nas formas cardíaca e digestória exclusivas ou combinadas elas são comumente mais pronunciadas. Na dependência da sua maior ou menor severidade, estas lesões podem resultar em variáveis graus de disfunção parassimpática e/ou simpática, principalmente a primeira. Apesar da crítica influência autonômica sobre o funcionamento cardiovascular, o significado fisiopatológico e clínico, notadamente em longo prazo, da disfunção autonômica cardíaca permanece desconhecido na doença de Chagas.

**Métodos:** Revisão sobre a disfunção autonômica cardíaca na doença de Chagas e suas potenciais consequências, como base para considerações acerca da possível relação entre este distúrbio e desfechos clínicos e funcionais globais e cardiovasculares desfavoráveis. **Resultados:** Os potenciais desfechos que a disautonomia cardíaca pode variavelmente determinar ou predispor na doença de Chagas incluem: arritmias transitórias ou sustentadas, morte súbita, mal prognóstico global e cardiovascular, morbi-mortalidade aumentada, deficiente adaptação cardiovascular a demandas funcionais e/ou em resposta a estímulos internos e externos por meio de ajustes da frequência cardíaca e outras variáveis hemodinâmicas, e distúrbios imunomoduladores e psico-funcionais. **Conclusões:** A alteração da modulação autonômica cardíaca na doença de Chagas pode não representar mero epifenômeno sem significado. Evidências indiretas sugerem papel importante desta alteração como fator predisponente ou determinante primário para o desenvolvimento secundário de distúrbios funcionais manifestos ou não e consequências clínicas cardiovasculares, e para a ocorrência de desfechos desfavoráveis.

**Palavras-chaves:** Cardiopatia chagásica crônica. Forma indeterminada da doença de Chagas. Função autonômica cardíaca. Disautonomia cardíaca. Desfechos cardiovasculares.

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### INTRODUCTION

The autonomic nervous system coordinates and modulates the harmonious and integrated functioning of the organism and its relations with the surrounding environment with fine precision. In particular, the autonomic influence on the heart and vascular system is one of the most remarkable and extensive homeostatic processes in the organism. Therefore, disturbances to this neural regulatory system, even subtle or not outwardly detectable ones, certainly affect to some extent the homeostasis of the organism with both short- and long-time functional prejudice. In recent years, various direct and indirect lines of evidence have emerged linking lesions and disturbances of this system to various cardiovascular functional alterations and to higher mortality and morbidity in many clinical conditions.

Lesions affecting the autonomic nervous system linked to the heart and consequent cardiac dysautonomia of variable degrees are a hallmark of Chagas disease. These lesions have been extensively demonstrated both in affected subjects and experimental animal models. On these grounds, it is reasonable to assume that the autonomic dysfunction in Chagas disease may represent an example of a homeostatic disturbance acutely and chronically expressed in different forms and to variable degrees, affecting among others, neural, cardiovascular, endocrine, renal, immunological and metabolic regulatory mechanisms. In this context, the characterisation of the functional and clinical significance of chagasic cardiac autonomic dysfunction is a critical issue. This aspect of the pathophysiology of Chagas disease is open to speculation, representing a question that remains to be fully clarified, even though more than a century has passed since the discovery of the disease. Several works have demonstrated that this disturbance result in significant loss of acute cardiovascular adaptation in response to different stimulus. On the other hand, virtually none observation exists showing that the cardiac autonomic dysfunction can result in important long-term cardiovascular and other functional consequences.

Therefore, it seems reasonable and timely to undertake an insightful consideration of the possible role of the cardiac autonomic dysfunction in chronic Chagas disease as a possible cause or contributing factor of some functional disturbances and clinical manifestations and as a determinant of adverse outcomes.

## CHAGAS DISEASE ESSENTIALS

Chagas disease is a very serious chronically debilitating and often fatal human endemic infectious-parasitic affection that is caused by the protozoan *Trypanosoma cruzi* and transmitted by hematophagous triatomid bugs. It usually victimises persons living in underdeveloped social and economic conditions in most South and Central America countries, which are endemic for the disease. A recently estimated cohort of about 8-10 million people living in these countries is chronically infected, thus carrying one of the chronic clinical forms of the disease. Around 50-60% of them lack evident manifestation and about 30-40% have obvious typical clinical and functional disturbances of the heart and/or digestive tract resulting in different, mild to severe consequences, with approximately estimated 6-12,000 deaths per year. Nearly 28 million people are at risk of to acquire the disease and the number of annual new cases due to vectorial transmission is close to 41,000<sup>1-4</sup>. As the result of migrating flow, thousands of infected Latin-American immigrants are also living in the United States, Canada, Australia, Japan and in several European countries. Indigenous cases are also present in many of these countries because of the geographical spreading of infected bugs by ecological and climatic changes. It is estimated in about 400,000 the number of infected subjects in these non-endemic countries<sup>5,6</sup>.

A myriad of unique and intriguing pathological, pathophysiological and clinical aspects regarding the heart and digestive tract are markers of Chagas disease. This disease manifests under an acute form, which is followed, usually after some decades, by one of the different chronic forms. The acute form often shows infectious nonspecific symptoms for a few days, or it may proceed to eventual myocarditis of variable severity. In the chronic form named indeterminate form, the diagnosis is based only on positive, specific serological tests. Most of the affected subjects remain in this form for their lifetime having excellent long-term prognoses, while showing clinical and functional normality as characterised at the primary diagnostic level by clinical examination, standard electrocardiogram (ECG) and X-rays (Rx) of the heart and digestive tract. However, some chagasics with this form show subtle cardiac functional disturbances detectable by more sophisticated and sensitive exams, such as Doppler echocardiography, 24h ECG, electrophysiological studies and autonomic tests<sup>1,4,7-10</sup>.

The other chronic forms, which may evolve or not from the indeterminate form, are the cardiac form, the digestive form, and the cardiac plus digestive associated form, expressing the exclusive or associate involvement of the heart and digestive tract. In these forms, the underlying pathological changes determining the clinical and functional manifestations are inflammatory and degenerative lesions and fibrosis of the affected structures, which occur with variable intensity and extension and progress gradually from an acute to a chronic pattern. In the heart, the structures exclusively or associatively affected are mainly the atrial and ventricular myocardium, the specialised electrical excitation and conduction tissue, the intrinsic neural network, the postganglionic autonomic

innervation and neurotransmitter cellular receptors, and the coronary microcirculation<sup>11-15</sup>.

During its course, the disease may show various specific clinical and/or functional manifestations with or without symptoms of variable severity and occurring exclusively or in association. These manifestations include systolic and/or diastolic dysfunction, heart enlargement with or without failure, a great variety of hypokinetic and hyperkinetic arrhythmias and other electrophysiological disturbances, cerebral or pulmonary thromboembolism, digestive megasyndromes, cardiac autonomic dysfunction and expected or unexpected sudden cardiac death. The form involving the heart shows high morbidity and mortality with considerable potential for short- and middle-term disability and poor prognosis in about 30-40% of affected subjects. At the primary level, the diagnosis of cardiac and digestive forms depends on finding alterations in a standard electrocardiogram and radiological signs of enlargement of the digestive tract segments, respectively, independently of the presence of clinical symptoms and signs, but in the presence of positive serology for the disease<sup>1,2,4,10,11,16,17-19</sup>.

## CARDIAC AUTONOMIC NERVOUS SYSTEM IN CHAGAS DISEASE

Diffuse damage to the autonomic nervous system, principally of the parasympathetic branch affecting the heart and digestive tract, is a remarkable pathological feature commonly present in variable degrees and extents in the acute and all chronic forms of human Chagas disease<sup>11,13,15,17-19</sup> and the corresponding forms of experimental *Trypanosoma cruzi* infection in different animal models<sup>20-24</sup>. This is a fact recognised soon after the description of the disease at the beginning of the past century. Autonomic damage expressed by neuronal and ganglionic inflammation and destruction with variable loss of nerve cells is credited to initiate in the acute phase and continue into the chronic phase, occurring through non-immune or parasitic and immune mechanisms acting exclusively or in combination<sup>11,15,25</sup>.

Many autonomic components, mainly related to functional modulation of the heart and digestive viscera, including central neural structures at different levels, peripheral extrinsic and intrinsic autonomic ganglia, afferent neurons from receptors, sympathetic and parasympathetic efferent neurons and the beta-adrenergic and muscarinic cholinergic neurotransmitter cellular receptors, may be injured exclusively or in combination, and this has been demonstrated both in human and experimental Chagas disease<sup>11,13,15,18,20-23,26-29</sup>.

Several studies have shown less pronounced lesions of the cardiac parasympathetic innervation in the indeterminate form, which are usually represented by discreet to moderate focal or zonal neuroganglionitis. In the isolated or associate cardiac and digestive forms of the disease, the intrinsic innervation of the heart is often more severely damaged by inflammatory and degenerative alterations. Moreover, a decrease in the number of cardiac ganglion cells and neurons has clearly been shown, and both parasympathetic and sympathetic lesions have been described<sup>11,13,15,18,21-24,28,30</sup>.

As expected from these pathological features, a particular functional disturbance in the different forms of Chagas disease is a variable impairment of the autonomic modulation of the involved organs, especially the heart and digestive tract. In the heart, the

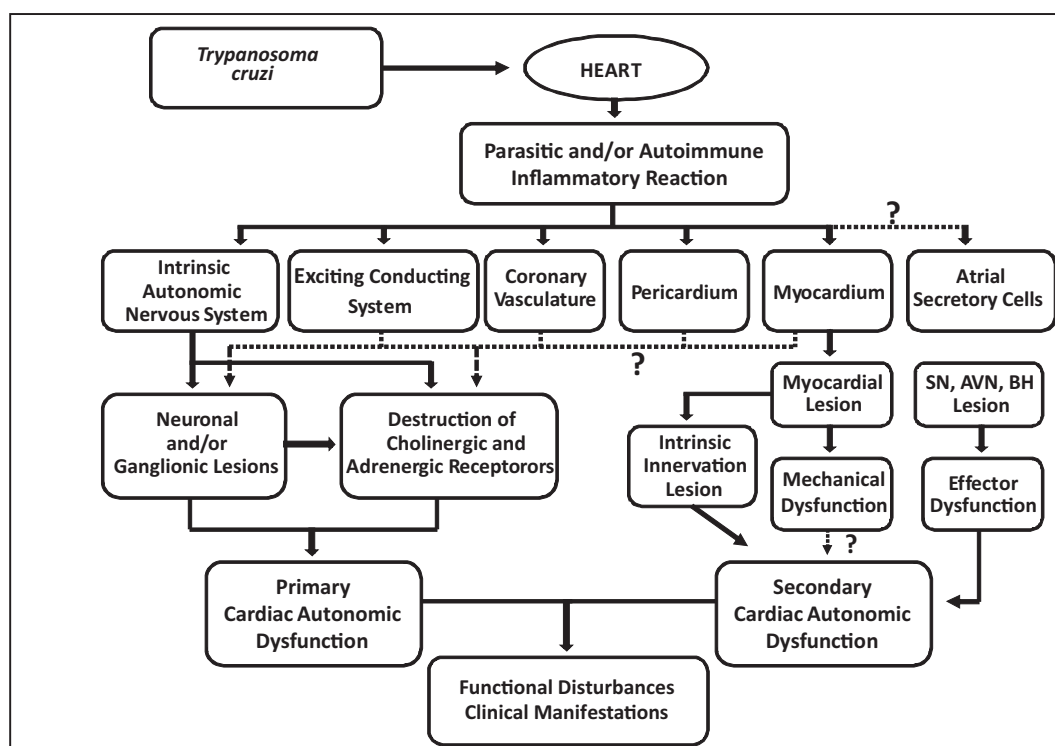
autonomic dysfunction may affect, exclusively or in combination, the electrical properties of the sinus and atrioventricular node and the intraventricular conducting system, as well as the electrical and mechanical properties of the atrial and ventricular myocardium. Classical autonomic tests and heart rate variability analysis have evaluated impairment of autonomic control exclusively on the sinus node. They have demonstrated that cardiac parasympathetic and/or sympathetic dysfunctions are present in many affected subject, being both observed not only in chagasics with exclusive or combined evident cardiomyopathy but also in those with the exclusive digestive form or without overt manifestations of heart or digestive damage. Normal autonomic modulation of the heart is also encountered in chagasics with any form of the disease. When present, the disturbance occurs with variable severity according to the chronic form of the disease and even between subjects affected with the same form<sup>8,9,17,30-37</sup>. Chronically infected children with the indeterminate form also show cardiac autonomic dysfunction<sup>38</sup>. Chagasics with arterial hypertension also present impaired cardiac parasympathetic modulation, apparently to the same extension as chagasics without hypertension<sup>39</sup>. However, a sample of elderly chagasics with the indeterminate form of the disease did not showed any alterations in cardiac autonomic function as compared with healthy elderly subjects<sup>40</sup>. Contrasting with this finding, elderly chagasics below 70 years, but not those older, with an uncharacterised form of the disease, show reduced vagal modulation<sup>41</sup>.

It seems that the intensity of the cardiac autonomic functional disturbance is strictly correlated with the clinical form of chagasic organic involvement. Usually, mild autonomic dysfunction occurs in the indeterminate form and in chagasics showing a borderline electrocardiogram, the severe disturbances occur in the cardiac-digestive and digestive forms, and moderate dysfunction occurs in the exclusive cardiac form<sup>8,10,32,33</sup>.

In addition to the lesions in different structures of the autonomic nervous system, exclusive degenerative and inflammatory damage in effectors of the autonomic influence on the heart, such as the sinus and atrioventricular nodes and the bundle of His may also occur with resultant secondary cardiac autonomic dysfunction<sup>42</sup>. Similarly, lesions in the myocardium may also result in disturbed autonomic modulation of atrial and ventricular electrical and mechanical properties. Cardiac and vascular mechanoreceptors, central and peripheral chemoreceptors and afferent neural fibres in the heart and lungs seem also to be damaged, which may impair cardiopulmonary baroreflexes and modify chemoreflex responses<sup>43,44</sup>.

The diagram in **Figure 1** shows proven and possible pathophysiological mechanisms of the cardiac autonomic dysfunction triggered by *Trypanosoma cruzi* infection, which may culminate in different clinical and functional manifestations.

Despite the extensively recognised and well-established disturbances of the autonomic nervous system, the pathophysiological



**FIGURE 1 -** *Trypanosoma cruzi* may affect, in combination or exclusively, all of the structures of the heart by means of toxicity or inflammatory effects, resulting in lesions that affect both the intrinsic autonomic innervation, the exciting-conducting system and the contractile myocardial fibres.

One of the important consequences is cardiac autonomic dysfunction, which has been repeatedly demonstrated to be a primary disturbance independent of contractile dysfunction. This impaired autonomic function may be the substrate for various secondary functional and clinical manifestations. The continuous lines show proven pathophysiological relationships, and the dotted lines show possible but unproven disturbances.

SN: sinus node; AVN: atrioventricular node; BH: bundle of His.

and clinical significance of the cardiac autonomic dysfunction remains one of the major challenges to overcome in Chagas disease research. No study has yet fully considered the short- and long-term prognostic significance, functional cardiovascular limitations and potential risks for adverse outcomes associated with the cardiac autonomic dysfunction, and many questions remain unanswered<sup>16</sup>. Is the cardiac autonomic dysfunction in Chagas disease a simple epiphenomenon without any functional, clinical or prognostic significance? Does it constitute a key physiopathogenetic link or triggering cause for the development of secondary disturbances and manifestations such as different arrhythmias, sudden death, and continuing contractile failure? Could it represent a risk factor for cardiovascular or general morbidity and mortality? Or, alternatively, is it an underlying mechanism for altered homeostasis imposing inappropriate short- and long-term cardiovascular adaptation to multiple internal or external stressful stimuli?

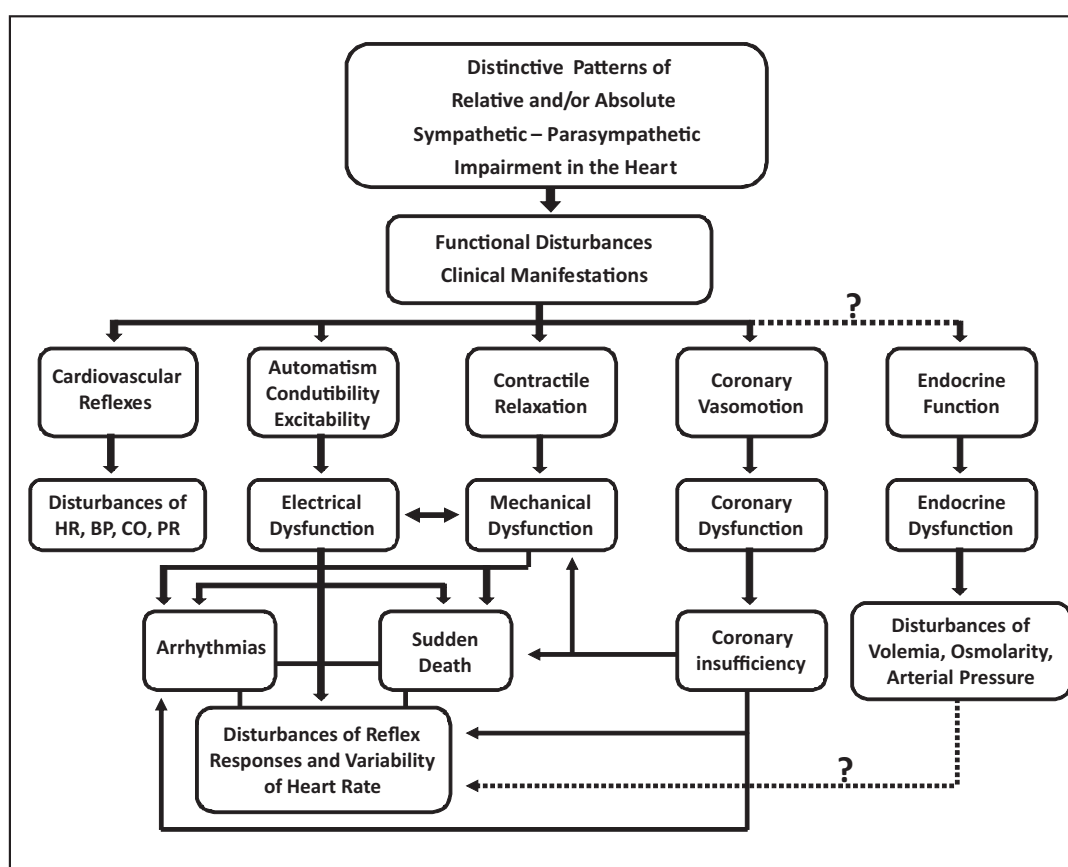
The role of cardiac autonomic dysfunction in determining these outcomes in Chagas disease probably is not a mere guess, but a real possibility, as we first hypothesised, considering the important influence of the autonomic nervous system on all the electrical and mechanical properties of the heart and on cardiovascular and general morbidity and mortality<sup>16,28,45,46</sup>. Also, several recent observations have emerged linking unfavourable cardiovascular outcomes to cardiac dysautonomia in various pathological conditions that affect the autonomic nervous system<sup>47-53</sup>.

**Figure 2** depicts possible clinical and functional disturbances likely to result or be influenced by impaired autonomic modulation on the different structures and functional properties of the heart.

## AUTONOMIC AND CONTRACTILE DYSFUNCTION

Regarding the possible relationship between ventricular and autonomic dysfunctions, it was originally proposed that cardiac autonomic denervation would be the direct and primary cause of the myocardial contractile deficiency and the advancement of this mechanical disturbance until the phase of congestive heart failure. This is the neurogenic theory of the physiopathogenesis of chronic Chagas heart disease, by which this condition would be a neurocardiopathy consequent to parasympathetic impairment, and therefore unbalanced sympathetic dominance would submit the heart to excessive adrenergic activity with resultant increasing organ deterioration and failure<sup>11</sup>.

However, a great number of subsequent pathological, functional and clinical studies have formed a widely accepted physiopathogenetic concept according to which cardiac autonomic denervation and the resultant functional disturbances are not the determining mechanism neither of the progressive cardiomegaly of Chagas disease nor the ensuing heart failure in the most cases. The progressive contractile



**FIGURE 2** - Sympathetic and parasympathetic impairments of variable degree may affect all the properties and functional mechanisms of the heart, resulting in electrical, mechanical, coronary and, possibly, endocrine dysfunctions.

As a consequence, distinctive functional and clinical disturbances or manifestations may occur, thereby conferring to the autonomic impairment potentially important pathophysiological and prognostic significance in Chagas disease. The solid lines show established mechanisms and the dashed lines show possible mechanisms underlying different cardiac pathological conditions.

HR: heart rate; BP: blood pressure; CO: cardiac output; PR: peripheral resistance.



dysfunction of the heart critically depends on the underlying evolutionary chronic fibrotic inflammation of the myocardium<sup>15,17,54</sup>. Therefore, the autonomic denervation and the consequent disturbance of neural heart control do not seem to be a direct cause of the contractile dysfunction<sup>19,34,37,55,56</sup>.

On the other hand, several lines of evidence have clearly proven that the progressive contractile mechanical disturbance does not result in secondary autonomic dysfunction, except in the phase of heart failure where this functional disturbance is present in variable degree. These evidences include the demonstration that contractile alteration of the right ventricle is independent of autonomic dysfunction<sup>34</sup>, parasympathetic impairment precedes the left ventricular systolic dysfunction<sup>35</sup>, and that chronotropic incompetence in response to exercise testing is an early warning of cardiac autonomic disturbance that is independent of ventricular function<sup>37</sup>. In addition, we observed pronounced sympathetic and parasympathetic depression with preserved sympathovagal balance as evaluated by short-term heart rate variability, which occurred with virtually unaltered morphological and functional ventricular echocardiographic parameters. The unique ventricular alteration was an increased left ventricular end systolic diameter, and this was directly associated with cardiac autonomic impairment. This marked imbalance between autonomic and ventricular dysfunction reinforces that there is no precise causal relationship between the two and that autonomic impairment may precede ventricular alterations in this disease<sup>37</sup>.

Therefore, all of these results suggest that cardiac autonomic impairment is a primary phenomenon, being neither a cause nor the result of the continuing chronic contractile dysfunction in Chagas heart disease. Despite this, it is not possible to eliminate the possibility that autonomic and contractile dysfunction mutually influence or worsen one another to some extension<sup>37,58</sup>. However, an isolated alternative hypothesis considers that cardiac autonomic dysfunction is the result of contractile ventricular dysfunction and other primary pathophysiological mechanisms<sup>59</sup>.

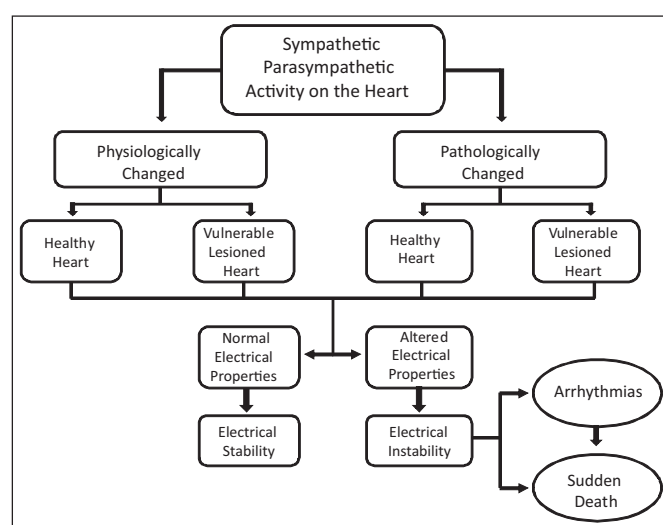
### DYSAUTONOMIC ARRHYTHMOGENESIS - A WORKING HYPOTHESIS

Based on the previous considerations, an expected attractive and logical implication of cardiac autonomic dysfunction as a determining or predisposing pathophysiological risk factor, perhaps one of higher relevance and clinical consequence, concerns the physiopathogenesis of arrhythmias and even sudden cardiac death<sup>16</sup>, which are so common in Chagas heart disease<sup>1,28,45,60,61</sup>.

Indeed, the autonomic nervous system critically modulates all of the electrophysiological properties of the electrical and contractile tissues of heart (automatism, conductivity and excitability) whose alterations are the underlying causes of arrhythmogenesis. The parasympathetic branch exerts depressive or stabilising anti-arrhythmogenic electrophysiological effects and a negative inotropism, while the sympathetic branch has a pro-arrhythmogenic stimulatory effect and exerts a positive inotropism; an adequate balance between these autonomic influences on the heart is essential for maintaining the electrical stability of the myocardium and the excitation and conducting system. Therefore, parasympathetic depression or sympathetic overactivity could increase the vulnerability to arrhythmogenesis. Consequently, changes of variable

degree affecting the sympathetic-parasympathetic balance on the heart in favour of absolute or relative sympathetic dominance may result in electrophysiological instability and induce arrhythmias of different types with a broad severity spectrum.

Changes in autonomic modulation can be triggered or exacerbated by different intrinsic or extrinsic factors involving the heart-brain relationship, such as primary neural and cardiac factors and a great sort of emotional, psychosocial and stressors factors. The arrhythmias can to generate even sudden death depending on the extent and speed of onset of such neurocardiac alterations and on the pathological and functional substrate of the myocardium and excitation and conducting tissues. It is possible that even physiological changes of the cardiac autonomic system acting on a damaged heart substrate are able to produce arrhythmias. **Figure 3** depicts these final common potential physiopathological mechanisms of arrhythmogenesis that can be provoked by sympathetic and/or parasympathetic changes or dysfunction.



**FIGURE 3 - Potential pathophysiological pathways of autonomic arrhythmogenesis.** Relative or absolute physiological or pathological changes in sympathetic and/or parasympathetic activity of the healthy or vulnerable heart may induce alterations in cardiac electrical properties potentially able to result in arrhythmias of variable severity and even sudden death.

In Chagas heart disease, isolated or combined lesions of variable magnitude and extent affecting the atrial and ventricular myocardium, the specialised excitation and conducting system and the intrinsic autonomic innervation of the heart especially propitiate the development of arrhythmias of different types, severity and duration, from which may arise life-threatening events resulting in unexpected or expected sudden death. Distinctive patterns of autonomic disturbances, associated or not with myocardial and specialised tissue lesions, are critically important considering their potential to cause or worsen changes in all the electrophysiological properties of heart, eventually triggering some kind of arrhythmia.

Hypothetically, the more discrete the autonomic dysfunction with subtle sympathetic-parasympathetic imbalances resulting from focal or zonal intrinsic neuroganglionic lesions, the higher is the vulnerability to arrhythmogenesis and the potential for unexpected sudden death, as commonly occurs in chagasic subjects with heart disease of mild to moderate severity and perhaps occasionally in those with the indeterminate form or a borderline electrocardiogram<sup>1,16,60,61</sup>. On the other hand, more pronounced autonomic impairment

resulting from marked and extensive lesions at different levels of the intrinsic nervous system may associate with a reduced chance of arrhythmogenesis and sudden death. Therefore, chagasics with relatively severe cardiac intrinsic autonomic denervation may be protected against the phenomenon of arrhythmogenesis, considering that in such cases the heart is practically disconnected from the extrinsic nervous system and is free of unbalanced autonomic influences on its electrophysiological properties resulting from internal or external stimuli<sup>16</sup>.

Some observations support the proposed hypothesis of dysautonomic arrhythmogenesis in Chagas disease. Studies from hearts with myocardial infarction and other lesions have raised the possibility that heterogeneous axonal regeneration and proliferation of sympathetic nerves following the damage may cause electrical heterogeneity and instability with consequent arrhythmias as a result of regional hyperinnervation or nerve sprouting<sup>62,63</sup>. The coexistence of denervated and hyperinnervated area in the damaged myocardium could result in increased electrophysiological heterogeneity during absolute or relative sympathetic overactivity of diverse origin leading to ventricular hyperkinetic arrhythmias<sup>63</sup>.

In this context, it is reasonable to hypothesise that in Chagas disease, the same pathophysiological mechanism may trigger arrhythmogenesis, considering the regional heterogeneity of the lesions in the intrinsic innervation<sup>11,13,22,30</sup> and in ventricular myocardium<sup>64</sup> of the chagasic heart. Indeed, an association between regional myocardial sympathetic denervation, detected by scintigraphy with <sup>123</sup>I-metaiodobenzylguanidine, and the occurrence of sustained ventricular tachycardia was observed in chagasic cardiomyopathy with preserved ventricular function<sup>64</sup>, and sympathetic modulation was noted to be affected in the ventricular myocardial also in chagasic subjects with the indeterminate form or borderline electrocardiogram<sup>65</sup>. In addition, cardiac sympathetic and cholinergic reinnervation was showed at least in experimental Chagas disease, and is likely that these phenomena occur in a regional heterogeneous manner resulting in unbalanced autonomic effect as a potential arrhythmogenic mechanism<sup>66,67</sup>. A finding of myocardial lesions similar to those induced by catecholaminogenic cardiotoxicity, which can represent a substrate for the induction of arrhythmias, in chagasic subjects without clinical manifestations who died suddenly and unexpectedly<sup>45</sup>, reinforces the hypothesis of dysautonomic arrhythmogenesis as a possible cause of sudden death in Chagas disease<sup>16</sup>.

In addition, observations of impaired cardiac autonomic modulation on the sinus node as detected by conventional linear or nonlinear heart rate variability analysis in subjects with Chagas heart disease have also stressed the possibility of a link between autonomic dysfunction and arrhythmias<sup>46,68</sup>. Moreover, several studies based on heart rate variability analysis in patients with coronary disease have showed that altered autonomic influence on the heart has a key role in the vulnerability, development and maintenance of life-threatening arrhythmias, which may result in sudden death<sup>49,50,69</sup>. A shift of the sympatho-vagal balance toward sympathetic dominance has been demonstrated before the beginning of arrhythmic events such as ventricular tachycardia and fibrillation<sup>50,62</sup>. Reduced complexity of heart rate variability as assessed by nonlinear dynamic analysis has also been noted before the initiation of ventricular tachyarrhythmias in patients with Chagas heart disease, suggesting impaired cardiac autonomic control as the underlying mechanism<sup>46</sup>. In Brugada

syndrome, subjects with autonomic dysfunction show syncope, aborted sudden death and arrhythmias more often than those without the disturbance<sup>53</sup>.

Nevertheless, one study in a cohort of Chagas heart disease subjects observed no prognostic prediction of a time-domain index of heart rate variability (SDNN-standard deviation of normal-to-normal heart intervals)<sup>70</sup>. However, this was the sole index evaluated in this study and was derived from series of ECG R-R intervals employing the 24h Holter monitoring, which methodologically show some restrictions limiting the heart rate variability analysis and interpretation. To this regard, it should be reinforced that there are abundant data supporting the prognostic significance and the role as risk marker of some classical linear and newer non-linear measures of heart variability in different clinical conditions other than Chagas disease<sup>48-52,69,71</sup>. But, several factors influence the prognostic value of heart rate variability measurements when they are used in risk stratification, which among the more important are: a) the type and combination of indexes, b) the nature of the autonomic modulation that the indexes reflect, if overall or parasympathetic or sympathetic exclusive or balanced one, c) the circadian rhythm of heart rate variability, d) the epoch of evaluation during the development of the clinical, functional or pathological condition analysed, e) the severity of left ventricular dysfunction, f) the method employed to achieve, process and editing the ECG R-R intervals series, if derived from 5min short-term recording in controlled experimental setting, or long-term ambulatory 24h Holter recording under uncontrolled interfering factors and non-stationary data series, g) the nature of the selected adverse outcome<sup>50,51,69,71</sup>.

## DISTURBED CARDIOVASCULAR HOMEOSTATIC NEURAL REGULATION

In diseases where the autonomic nervous system is involved, an important expected pathophysiologically and clinically significant effect of autonomic impairment may be inadequate short-term or long-term cardiovascular adaptation to different stimuli or functional conditions. This functional failure may be the result of compromised electrophysiological and mechanical tonic and reflex responses of the heart, which mainly affect heart rate, blood pressure, peripheral resistance, venous return and cardiac output. Underlying this adaptive inability is a relative or absolute impairment of sympathetic and parasympathetic cardiac modulation, which results in reduced homeostatic capacity and vulnerability to functional disturbances or detrimental effects of certain internal and external stimuli.

In Chagas disease subjects without heart failure, poor cardiovascular adjustment has been observed in steady-state and in connection with different transient functional conditions as result of altered reflex mechanisms. Deficient chronotropic responses have been noted during both dynamic<sup>57,72</sup> and isometric<sup>73</sup> exercise in chagasics with heart disease. The inability to achieve adequate tachycardia and blood pressure stabilisation upon standing has also been demonstrated<sup>74-76</sup>. Depressed sensitivity of the baroreflex mechanism resulting in blunted bradycardia or tachycardia in response to acute elevation or reduction of arterial pressure has been observed<sup>32,77</sup>, as have altered baroreflex responses traduced by deficient heart rate responses during and after the Valsalva manoeuvre in chagasics with any form of the disease<sup>8,33,36,78,79</sup>. Additionally,

moment-to-moment heart rate variability is variably depressed in chagasic subjects both in supine and standing positions<sup>9,10,39,41,46,68,80</sup>. These autonomic cardiovascular disturbances occur most often in chagasics with exclusive or combined heart disease. Therefore, in people with Chagas disease, deficiencies in short- and long-term autonomic adjustments of hemodynamic variables in response to different functional demands or to stressful physiological or psychological stimuli might affect the efficiency and accuracy of moment-to-moment cardiovascular adaptation. These individuals may be unable to adequately perform their physical and physiological activities, they may reveal subtle or evident manifestations of poor cardiovascular health, and they may still exhibit the substrate for continuous development of cardiovascular disturbances<sup>16</sup>. In fact, several observations suggest that alterations of autonomic regulatory physiological processes or influences responsible for cardiovascular adaptation dynamics may be a mechanism for the development of functional derangements and disease states<sup>81-83</sup>.

Finally, recent findings have shown a positive correlation between reduced heart rate variability caused by autonomic impairment and poor prognosis represented by increased morbidity and mortality in coronary disease, diabetes mellitus, heart failure and non-coronary sudden death; that is, the more heart rate variability is depressed, the worse the outcome<sup>48-52,69,84</sup>. In this context, it is likewise possible that the loss of homeostatic adaptive capacity dependent on changes in heart rate consequent to permanently impaired cardiac autonomic modulation capacity in Chagas disease may contribute to its progression and to increase of the cardiovascular and overall mortality and morbidity of affected subjects.

#### OTHER POSSIBLE EFFECTS OF AUTONOMIC DYSFUNCTION

Besides the cardiac involvement, systemic autonomic lesions also occur in Chagas disease<sup>11</sup> and may affect metabolic, renal and endocrine mechanisms and certain homeostatic controls. Moreover, considering the intricate relationship between different organ systems and processes, the proper cardiac autonomic dysfunction is expected to be correlated with metabolic, hormonal and functional renal disturbances. Indeed, cardiac autonomic dysfunction has been observed in chagasic subjects with either indeterminate or cardiac forms of the disease and in experimentally *Trypanosoma cruzi*-infected animals simultaneously with altered osmoregulation dependent on the antidiuretic hormone response<sup>85</sup>, altered hydroelectrolytic balance<sup>86</sup> and altered glucose tolerance<sup>87</sup>.

Another possible pathophysiological role of chagasic autonomic dysfunction, irrespective of the organ involved, concerns the induction of immunomodulatory disturbances and alterations of immunological mechanisms participating in the defence against the parasite responsible for the disease<sup>25</sup>. Recent evidence shows that the autonomic nervous system significantly modulates processes implicated in cellular and humoral immunity as a consequence of the close anatomical and functional relationship between this system and the immune system<sup>88</sup>. This finding raises the possibility that the autonomic dysfunction associated with chagasic infection could be an influential or determining cause of immunological alterations contributing to the development and maintenance of chronic Chagas chronic infection. In this regard, an association between cardiac autonomic dysfunction and altered levels of cytokines was recently

demonstrated in chagasics with the indeterminate and cardiac forms and with sustained parasitemia; the heart disease patients showed higher concentrations of IL-10 and lower IFN- $\gamma$ , suggesting some disturbance of the process of immune regulation<sup>89</sup>.

Difficulty in coping with social stress and in controlling emotions can also occur in subjects with systemic autonomic impairment or even in just cardiac autonomic impairment, because the integrity of parasympathetic homeostatic function is important for the adequate performance of these tasks, and the heart is crucial to providing functional adaptation for them<sup>82,83,90</sup>. Therefore, chagasic subjects may also be susceptible to psycho-functional derangements attendant on functional demands for higher cerebral processes in association with their autonomic cardiovascular adaptive disability, as suggested by some evidences<sup>91,92</sup>. In fact, at least in other clinical conditions as the Alzheimer's disease, cognitive status and cardiac autonomic modulation evaluated by heart rate variability appear to be correlated in the sense that people with lower cardiac parasympathetic modulation and tendency for higher sympathetic modulation show more severe cognitive deficiencies<sup>93</sup>.

#### IMPLICATIONS FOR TREATMENT

If some functional and clinical manifestations of Chagas disease can be shown to be related in some extent to cardiac autonomic impairment, a perspective based on treatment of this disturbance emerges for the control or prevention of these manifestations and expectative of improving outcomes and more favourable long-term prognostic. At present, no effective treatment exists for chagasic cardiac autonomic dysfunction and some kind of therapy has rarely been evaluated.

In one study, re-establishing of altered blood pressure and heart rate responses to various autonomic tests, reduction of arrhythmias and other beneficial effects were observed after administering Cronassial®, a mixture of neuroregenerator gangliosides<sup>94,95</sup>. This agent, however, showed questionable security and has not been employed. Stem-cell therapy is a potential means of repairing injured cardiac autonomic intrinsic innervation<sup>96</sup>, but it has not yet proven to be effective and practical, and their effectiveness and application has actually an uncertain expectative.

Use of beta-blockers and other drugs that directly affect autonomic modulation by increasing parasympathetic activity and/or reducing sympathetic activity is a logical and reasonable alternative to be investigated. In this context, it is possible that beneficial effects of beta-blockers on the hemodynamic status, outcomes and mortality of chagasic patients with heart failure<sup>97</sup> be at least in part to the improvement of cardiac autonomic modulation. With respect to the alpha-beta-blocker drug carvedilol, one study in our laboratory demonstrated that when this drug was administered to subjects with heart failure due to Chagas disease<sup>98</sup> or other aetiologies<sup>99</sup>, improvement of depressed cardiac autonomic modulation was observed, as evidenced by enhanced heart rate variability associate with better hemodynamic and clinical status. In other study in chagasics with cardiomyopathy and heart failure, the same functional cardiac and clinical benefits were observed after addition of carvedilol to conventional therapy<sup>100</sup>. Therefore, knowledge about the cardiac autonomic dysfunction in Chagas disease has implications that reach far beyond its functional and clinical significance.



## CONCLUDING REMARKS AND PERSPECTIVES

In spite of the significant advances achieved in more than one century of research since the discovery of the disease, the functional and clinical implications of the cardiac autonomic impairment in Chagas disease are incompletely understood and can only be conjectured. There are few substantial direct pathological, pathophysiological, clinical or epidemiological findings linking variable degrees of cardiac autonomic dysfunction with any other disturbance or clinical manifestation of Chagas disease, although the real likelihood of such a relationship. However, several indirect lines of evidence point to a likely important role of the cardiac autonomic dysfunction as a primary trigger or mediator favouring the development of various cardiovascular functional disturbances and the emergence of certain clinical consequences, thereby influencing cardiovascular outcomes and mortality.

The possible effects that evident or subtle cardiac autonomic dysfunction might variably provoke in subjects affected by Chagas disease include transient arrhythmic events or sustained arrhythmias, sudden cardiac death, adverse general and cardiovascular prognosis, and incompetence of cardiovascular system to adequately adapt via quick and moment-to-moment heart rate variations and changes in other hemodynamic variables to meet functional demands or to respond to internal or external stimuli. The hypothesis of dysautonomic arrhythmogenesis is proposed on the basis of an unbalanced sympathetic and parasympathetic autonomic activity or heterogeneous influence of one and other acting on an injured myocardial and/or excitation and conducting tissue. Although these consequences are straightforward and expected for chagasics with heart disease of any severity, for those with the indeterminate form, the validity of these effects is a more difficult question considering the discreteness of the cardiac autonomic impairment when present and the good long-term prognosis of this form of the disease<sup>1,7-10</sup>.

Impaired autonomic modulation of the heart in Chagas disease might not be a mere epiphenomenon without significance, and it is intuitive and reasonable to assume that it can be a somewhat important primary predisposing or triggering cause or marker of different, subtle or evident secondary functional disturbances and clinical manifestations. Well-controlled transverse and longitudinal studies are expected to be undertaken focusing on elucidating the pathophysiology, clinical manifestations and significance of chagasic cardiac autonomic dysfunction, especially concerning arrhythmogenesis, sudden death and continuing contractile deterioration. Another important line of research is evaluating the extent to which disrupted cardiovascular adaptive homeostasis deriving from autonomic impairment is a risk factor for general morbidity and mortality and adverse clinical outcome in the different forms of Chagas disease.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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